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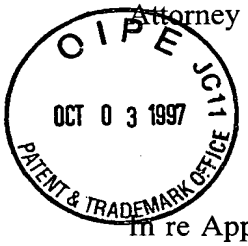
Attorney Docket No.: 5367.200-US

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#5 A.R.
04/01/98

In re Application of: Knudsen et al.

Serial No.: 08/922,200 Group Art Unit: To Be Assigned

Filed: September 2, 1997 Examiner: To Be Assigned

For: GLP-2 Derivatives

CLAIM TO CONVENTION PRIORITY UNDER 35 U.S.C. 119

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In the matter of the above-identified application and under the provisions of 35 U.S.C. 119 and 37 C.F.R. 1.55, Applicants claim priority of application Serial Nos. 0931/96 filed on August 30, 1996 in Denmark and 1259/96 filed on November 8, 1996 in Denmark. Applicants submit a duly certified copies of said foreign applications.

Respectfully submitted,

Date: October 1, 1997

Valeta A. Gregg

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Attorney Docket No.: 5367.200-US PATENT

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CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

I hereby certify that the attached correspondence comprising:

1. Claim to Convention Priority
2. 2 Original Priority Documents

is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

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Washington, DC 20231

on October 1, 1997.

Valeta A. Gregg
(name of person mailing paper)

Valeta A. Gregg
(signature of person mailing paper)

Kongeriget Danmark

Patent application No.: 0931/96

Date of filing: 30 Aug 1996

Applicant: Novo Nordisk A/S, Novo Allé, 2880 Bagsværd, DK

This is to certify the correctness of the following information:

The attached photocopy is a true copy of the following document:

- The specification and claims as filed with the application on the filing date indicated above.

Patentdirektoratet · Kongeriget Danmark

Erhvervsministeriet
Patentdirektoratet

TAASTRUP 03 Sep 1997

Jytte Hansen

Jytte Hansen
Kontorfuldmægtig

GLP DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel derivatives of glucagon-like peptides (GLP), in particular GLP-1 and GLP-2 and fragments thereof and analogues of such fragments which have a protracted profile of action and to methods of making and using them.

BACKGROUND OF THE INVENTION

Polypeptides are widely used in medical practice and since they can be produced by recombinant DNA technology it can be expected that their importance will increase also in the years to come. When native polypeptides or analogues thereof are used in therapy it is generally found that they have a high clearance. A high clearance of a therapeutic agent is inconvenient in cases where it is desired to maintain a high blood level thereof over a prolonged period of time since repeated administrations will then be necessary. Examples of polypeptides which have a high clearance are: ACTH, corticotropin-releasing factor, angiotensin, calcitonin, insulin, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, insulin-like growth factor-1, insulin growth factor-2, gastric inhibitory peptide, growth hormone-releasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostatin, somatotropin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opiods and analogues thereof, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminase, adenosine deaminase and ribonuclease. Although it has in some cases been possible to influence the release profile of polypeptides by applying suitable pharmaceutical compositions this approach has various shortcomings and is not generally applicable.

Although the interesting pharmacological properties of the fragment of glucagon-like peptide-1 known as GLP-1 (7-37) and analogues thereof have attracted much attention in recent years only little is known about the structure of these molecules. The secondary structure of GLP-1 in micelles has been described by Thorton et al. (*Biochemistry* **33** 3532-3539 (1994)) but a tertiary structure can not be ascribed to the molecule and GLP-1 is indeed a very flexible molecule. Since

their high clearance seriously limits the usefulness of these compounds the treatment of diabetes there still is a need for improvements in this field .

SUMMARY OF THE INVENTION

In its broadest aspect, the present invention relates to derivatives of GLP and fragments thereof and their analogues. Such derivatives have interesting pharmacological properties. Details of the invention are apparent from the claims.

Pharmaceutical compositions

Pharmaceutical compositions containing a polypeptide derivative according to the present invention may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a powder or a liquid for the administration of the polypeptide derivative in the form of a nasal or pulmonal spray. As a still further option, it may also be possible to administer the polypeptide derivative transdermally.

Pharmaceutical compositions containing a polypeptide derivative of the present invention may be prepared by conventional techniques, e.g. as described in Remington's Pharmaceutical Sciences, 1985.

Thus, the injectable compositions of the polypeptide derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.

Thus, according to one procedure, the polypeptide derivative is dissolved in an amount of water which is somewhat less than the final volume of the composition to be prepared. An isotonic agent, a preservative and a buffer is added as required and the pH value of the solution is adjusted - if necessary - using an acid, e.g. hydrochloric acid, or a base, e.g. aqueous sodium hydroxide as

needed. Finally, the volume of the solution is adjusted with water to give the desired concentration of the ingredients.

Examples of isotonic agents are sodium chloride, mannitol and glycerol.

Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol.

Examples of suitable buffers are sodium acetate and sodium phosphate.

A composition for nasal administration of certain polypeptides may, for example, be prepared as described in European Patent No. 272097 (to Novo Nordisk A/S) or in WO 93/18785.

According to some embodiments of the present invention, the GLP-1 component is provided in the form of an injectable solution. In such embodiments, the solutions preferably contain not less than about 2 mg/ml, preferably not less than about 5 mg/ml, more preferred not less than about 10 mg/ml of the GLP-1 component and, preferably, not more than about 100 mg/ml of the GLP-1 component. Similarly, injectable solutions of the insulin component are generally such solutions which are generally known in the art.

The polypeptide derivatives of this invention can be used in the treatment of various diseases. The particular polypeptide derivative to be used and the optimal dose level for any patient will depend on the disease to be treated and on a variety of factors including the efficacy of the specific peptide derivative employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case. It is recommended that the dosage of the polypeptide derivative of this invention be determined for each individual patient by those skilled in the art in a similar way as for known parent polypeptides.

In particular, it is envisaged that the derivatized GLP-1 component will be useful for the preparation of a medicament with protracted action/effect for the treatment of non-insulin dependent diabetes mellitus and/or for the treatment of obesity.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof,

be material for realizing the invention in diverse forms thereof.

1. A GLP derivative comprising a lipophilic substituent attached to any one amino acid residue with the proviso that only if the substituent has an ω-carboxylic acid group or is an alkyl group can it be attached to the N-terminal or C-terminal amino acid residue of the parent polypeptide.

2. A GLP derivative according to claim 1, wherein the lipophilic substituent comprises from 4 to 40 carbon atoms, more preferred from 8 to 25.

3. A GLP derivative according to claim 1, wherein said lipophilic substituent is attached to said amino acid in such a way that a carboxyl group of the lipophilic substituent forms an amide bond with an amino group of the amino acid.

4. A GLP derivative according to claim 1, wherein said lipophilic substituent is attached to said amino acid in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid.

5. A GLP derivative according to claim 1, wherein the lipophilic substituent is attached to the parent polypeptide by means of a spacer.

6. A GLP derivative according to claim 5, wherein the spacer is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, preferably two methylene groups which forms a bridge between an amino group of the parent polypeptide and an amino group of the lipophilic substituent.

7. A GLP derivative according to claim 5, wherein the spacer is an amino acid residue except Cys, or a dipeptide such as Gly-Lys.

8. A GLP derivative according to claim 7, wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of Lys or a dipeptide containing a Lys residue, and

the other amino group of the Lys or a dipeptide containing a Lys residue forms an amide bond with a carboxyl group of the lipophilic substituent.

9. A GLP derivative according to claim 7, wherein an amino group of the parent polypeptide forms an amide bond with a carboxylic group of the amino acid or dipeptide spacer, and an amino group of the amino acid or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

10. A GLP derivative according to claim 7, wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of the amino acid or dipeptide spacer, and the carboxyl group of the amino acid or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent.

11. A GLP derivative according to claim 7, wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of Asp or Glu, or a dipeptide containing an Asp or Glu residue, and a carboxyl group of the spacer forms an amide bond with an amino group of the lipophilic substituent.

12. A GLP derivative according to any of claims 1-4, wherein the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

13. A GLP derivative according to any of claims 1-4, wherein the lipophilic substituent is an straight-chain or branched alkyl group.

14. A GLP derivative according to any of claims 1-5, 8 and 9 wherein the lipophilic substituent is the acyl group of a straight-chain or branched fatty acid.

15. A GLP derivative according to claim 14 wherein the acyl group is selected from the group comprising $CH_3(CH_2)_nCO$-, wherein n is 4 to 38, preferably $CH_3(CH_2)_6CO$-, $CH_3(CH_2)_8CO$-, $CH_3(CH_2)_{10}CO$-, $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-.

16. A GLP derivative according to any of claims 1-5, 8 and 9 wherein the lipophilic substituent is an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid.

17. A GLP derivative according to claim 16 wherein the acyl group is selected from the group comprising $HOOC(CH_2)_mCO$-, wherein m is 4 to 38, preferably $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- and $HOOC(CH_2)_{22}CO$-.

18. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $CH_3(CH_2)_p((CH_2)_qCOOH)CHNH\text{-}CO(CH_2)_2CO$-, wherein p and q are integers and p+q is an integer of from 8 to 40, preferably from 12 to 35.

19. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophiic substituent is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO$-, wherein r is an integer of from 10 to 24.

20. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO$-, wherein s is an integer of from 8 to 24.

21. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO$- wherein t is an integer of from 8 to 24.

22. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer of from 8 to 18.

23. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}COCH((CH_2)_2COOH)NH\text{-}CO(CH_2)_wCH_3$, wherein w is an integer of from 10 to 16.

24. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NH\text{-}CO(CH_2)_xCH_3$, wherein x is an integer of from 10 to 16.

25. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NHCO(CH_2)_yCH_3$,

wherein y is zero or an integer of from 1 to 22.

26. A GLP derivative according to any of the preceding claims which has one lipophilic substituent.

27. A GLP derivative according to any one of claims 1-25 which has two lipophilic substituents.

28. A GLP derivative according to any of claims 1-27, wherein the parent polypeptide is selected from the group comprising GLP-1(1-45) or an analogue or a fragment thereof.

29. A GLP-1 derivative according to claim 28, selected from the group comprising GLP-1(7-35), GLP-1(7-36), GLP-1(7-36)amide, GLP-1(7-37), GLP-1(7-38), GLP-1(7-39), GLP-1(7-40) and GLP-1(7-41) and an analogue thereof.

30. A GLP-1 derivative according to claim 28, selected from the group comprising GLP-1(1-35), GLP-1(1-36), GLP-1(1-36)amide, GLP-1(1-37), GLP-1(1-38), GLP-1(1-39), GLP-1(1-40) and GLP-1(1-41) and an analogue thereof.

31. A GLP-1 derivative according to any of the claims 28-30 wherein the designation analogue comprises derivatives wherein a total of up to ten amino acid residues have been exchanged with any α-amino acid residue.

32. A GLP-1 derivative according to any of the preceding claims wherein the parent polypeptide is selected from the group comprising Arg^{26}-GLP-1(7-37), Arg^{34}-GLP-1(7-37), Lys^{36}-GLP-1(7-37), $Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Arg^{26,34}Lys^{39}$-GLP-1(7-39), $Arg^{26,34}Lys^{40}$-GLP-1(7-40), $Arg^{26}Lys^{36}$-GLP-1(7-37), $Arg^{34}Lys^{36}$-GLP-1(7-37), $Arg^{26}Lys^{39}$-GLP-1(7-39), $Arg^{34}Lys^{40}$-GLP-1(7-40), $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39), $Arg^{26,34}Lys^{36,40}$-GLP-1(7-40), Gly^{8}Arg26-GLP-1(7-37), $Gly^{8}Arg^{34}$-GLP-1(7-37), $Gly^{8}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39), $Gly^{8}Arg^{26,34}Lys^{40}$-GLP-1(7-40), $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39), $Gly^{8}Arg^{34}Lys^{40}$-GLP-1(7-40), $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39)and $Gly^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40).

33. A GLP-1 derivative according to claim 28, which is selected from the group consisting of

Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-37);

Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-37);

$Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-37);

Gly^{8}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-37);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-37);

Arg^{26}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-37);

Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-36);

Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-36);

$Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-36);

Gly^{8}, Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-36);

Gly^{8}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-36);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-36);

Arg^{26}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-36);

Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-35);

Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-35);

$Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-35);

Gly^{8}, Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-35);

Gly^{8}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-35);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-35);

Arg^{26}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-35);

Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-36)amide;

Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8}, Lys^{26}(N-ε-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8}, $Lys^{26,34}$-bis(N-ε-tetradecanoyl)-GLP-1(7-36)amide;

Arg^{26}, Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8}, Arg^{26},Lys^{34}(N-ε-tetradecanoyl)-GLP-1(7-37);

Lys^{26}(N-ε-tetradecanoyl), Arg^{34}-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-tetradecanoyl), Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$, Lys^{36}(N-ε-tetradecanoyl)-GLP-1(7-37);

Gly^{8}, $Arg^{26,34}$, Lys^{36}(N-ε-tetradecanoyl)-GLP-1(7-37);

Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8}, Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8}, Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8}, Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8}, Lys^{26}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8}, Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Arg^{26}, Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8}, Arg^{26},Lys^{34}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{26}(N-ε-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$, Lys^{36}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8}, $Arg^{26,34}$, Lys^{36}(N-ε-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

Arg^{26}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-36);

Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8}, Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-36);

Arg^{26}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-36);

Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-35);

Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8}, Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-35);

Arg^{26}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-35);

Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-36)amide;

Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{26}(N-ε-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(7-deoxycholoyl))-GLP-1(7-36)amide;

Arg^{26}, Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8}, Arg^{26},Lys^{34}(N-ε-(7-deoxycholoyl))-GLP-1(7-37);

Lys^{26}(N-ε-(7-deoxycholoyl)) Arg^{34}-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(7-deoxycholoyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$, Lys^{36}(N-ε-(7-deoxycholoyl))-GLP-1(7-37); and

Gly^{8}, $Arg^{26,34}$, Lys^{36}(N-ε-(7-deoxycholoyl))-GLP-1(7-37).

Lys^{26}(N-ε-(choloyl))-GLP-1(7-37);

Lys^{34}(N-ε-(choloyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(choloyl))-GLP-1(7-37);

Gly^{8}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-37);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-37);

Arg^{26}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-37);

Lys^{26}(N-ε-(choloyl))-GLP-1(7-36);

Lys^{34}(N-ε-(choloyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-36);

Gly^{8}, Lys^{26}(N-ε-(choloyl))-GLP-1(7-36);

Gly^{8}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-36);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-36);

Arg^{26}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-36);

Lys^{26}(N-ε-(choloyl))-GLP-1(7-35);

Lys^{34}(N-ε-(choloyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-35);

Gly^{8}, Lys^{26}(N-ε-(choloyl))-GLP-1(7-35);

Gly^{8}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-35);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-35);

Arg^{26}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-35);

Lys^{26}(N-ε-(choloyl))-GLP-1(7-36)amide;

Lys^{34}(N-ε-(choloyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{26}(N-ε-(choloyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-36)amide;

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(choloyl))-GLP-1(7-36)amide;

Arg^{26}, Lys^{34}(N-ε-(choloyl))-GLP-1(7-36)amide;

Gly^{8}, Arg^{26},Lys^{34}(N-ε-(choloyl))-GLP-1(7-37);

Lys^{26}(N-ε-(choloyl)) Arg^{34}-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(choloyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$, Lys^{36}(N-ε-(choloyl))-GLP-1(7-37);

Gly^{8}, $Arg^{26,34}$, Lys^{36}(N-ε-(choloyl))-GLP-1(7-37);

Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-37);

Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-37);

Gly^{8}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-37);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-37);

Arg^{26}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-37);

Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-36);

Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-36);

Gly^{8}, Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-36);

Gly^{8}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-36);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-36);

Arg^{26}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-36);

Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-35);

Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-35);

Gly^{8}, Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-35);

Gly^{8}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-35);

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-35);

Arg^{26}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-35);

Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-36)amide;

Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{26}(N-ε-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8}, $Lys^{26,34}$-bis(N-ε-(lithocholoyl))-GLP-1(7-36)amide;

Arg^{26}, Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8}, Arg^{26},Lys^{34}(N-ε-(lithocholoyl))-GLP-1(7-37);

Lys^{26}(N-ε-(lithocholoyl)) Arg^{34}-GLP-1(7-37);

Gly^{8}, Lys^{26}(N-ε-(lithocholoyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$, Lys^{36}(N-ε-(lithocholoyl))-GLP-1(7-37) and

Gly^{8}, $Arg^{26,34}$, Lys^{36}(N-ε-(lithocholoyl))-GLP-1(7-37).

34. A GLP derivative according to any of claims 1-26, wherein the parent polypeptide is selected from the group comprising GLP-2(1-35) or an analogue or a fragment thereof.

35. A GLP-2 derivative according to claim 34, selected from the group comprising GLP-2(1-30), GLP-2(1-31), GLP-2(1-32), GLP-2(1-33), GLP-2(1-34) and GLP-2(1-35).

36. A GLP-2 derivative according to any of the claims 34 and 35 wherein the designation analogue comprises derivatives wherein a total of up to ten amino acid residues have been exchanged with any α-amino acid residue.

37. A GLP-2 derivative according to any of the claims 1-27 and 34-36 wherein the parent polypeptide is selected from the group comprising Lys^{20}-GLP-2(1-33), $Lys^{20}Arg^{30}$-GLP-2(1-33), $Arg^{30}Lys^{35}$-GLP-2(1-35), $Arg^{30,35}Lys^{20}$-GLP-2(1-35), Arg^{35}-GLP-2(1-35), $Arg^{30}Lys^{34}$-GLP-2(1-34).

38. A GLP-2 derivative according to claim 34, which is selected from the group consisting of

Lys^{20}(N-ε-tetradecanoyl)-GLP-2(1-33);

$Lys^{20,30}$-bis(N-ε-tetradecanoyl)-GLP-2(1-33);

Lys^{20}(N-ε-tetradecanoyl)-Arg^{30}-GLP-2(1-33);

$Arg^{30}Lys^{35}$(N-ε-tetradecanoyl)-GLP-2(1-35);

$Arg^{30,35}Lys^{20}$(N-ε-tetradecanoyl)-GLP-2(1-35);

$Arg^{35}Lys^{30}$(N-ε-tetradecanoyl)-GLP-2(1-35);

$Arg^{30}Lys^{34}$(N-ε-tetradecanoyl)-GLP-2(1-34);

Lys^{20}(N-ε-(ω-carboxynonadecanoyl))-GLP-2(1-33);

$Lys^{20,30}$-bis(N-ε-(ω-carboxynonadecanoyl))-GLP-2(1-33);

Lys^{20}(N-ε-(ω-carboxynonadecanoyl))-Arg^{30}-GLP-2(1-33);

$Arg^{30}Lys^{35}$(N-ε-(ω-carboxynonadecanoyl))-GLP-2(1-35);

$Arg^{30,35}Lys^{20}$(N-ε-(ω-carboxynonadecanoyl))-GLP-2(1-35);

$Arg^{35}Lys^{30}$(N-ε-(ω-carboxynonadecanoyl))-GLP-2(1-35);

$Arg^{30}Lys^{34}$(N-ε-(ω-carboxynonadecanoyl))-GLP-2(1-34).

39. A pharmaceutical composition comprising a GLP derivative according to any of the preceding claims and a pharmaceutically acceptable vehicle or carrier.

40. Use of a GLP derivative according to any of the preceding claims for the preparation of a medicament with protracted effect.

41. Use of a GLP-1 derivative according to any of claims 28-33 for the preparation of a medicament with protracted effect for the treatment of non-insulin dependent diabetes mellitus.

42. Use of a GLP-1 derivative according to any of claims 28-33 for the preparation of a medicament with protracted effect for the treatment of insulin dependent diabetes mellitus.

43. Use of a GLP-1 according to any of claims 28-33 for the preparation of a medicament with protracted effect for the treatment of obesity.

44. Use of a GLP-2 according to any of claims 36-40 for the preparation of a medicament with protracted effect for the treatment of obesity.

45. Use of a GLP-2 according to any of claims 36-40 for the preparation of a medicament with protracted effect for the treatment of small bowel syndrome.

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